

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of	)	
	)	
Scott K. Kuwada	)	Art Unit: 1628
	)	
Application No. 10/505,244	)	Examiner: Pagonakis, Anna
	)	
Filing Date: January 18, 2005	)	Confirmation No. 7587
	)	
For: COMPOSITIONS AND METHODS FOR	)	
INHIBITING NF-KB MEDIATED	)	
TUMORIGENICITY AND ADHESION-	)	
DEPENDENT SURVIVAL OF	)	
CANCER CELLS	)	

**DECLARATION OF SCOTT KUWADA UNDER 37 C.F.R. §1.132**

Mail Stop RCE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

BALLARD SPAHR LLP  
  
Customer Number 23859

I Scott Kuwada, a Citizen of the United States of America, to hereby declare that:

1. I received my B.A. degree in biology from Whitman College 1980. I earned my MS in Biochemistry and MD degree in 1988 from the University of Hawaii John A. Burns School of Medicine. I completed an internal medicine residency at the Mayo Clinic in 1991 and a fellowship in Gastroenterology at the Mayo Clinic in 1994. I was appointed as an Assistant Professor of Medicine at the University of Utah in 1994, promoted to Associate Professor of Medicine & Adjunct Associate Professor of Oncological Sciences with tenure in 2004 and then Professor of Medicine & Adjunct Professor of Bioengineering in 2008. I was the Program Director of the Gastroenterology Fellowship Training Program from 1998-2008 and the Acting Chief of the Division of Gastroenterology from 2001-2003. In 2008, I accepted a position as Professor of Medicine and Chief of Gastroenterology at the University of Hawaii John A. Burns School of Medicine.

2. I began my research training in the laboratory of Dr. Frederick C. Greenwood and Dr. Gillian Bryant-Greenwood at the University of Hawaii in 1996-1998 and then in the laboratory of Dr. Nita Maihle at the Mayo Clinic from 1992-1993. I then spent 3 years in the laboratory of Dr. H. Steven Wiley at the University of Utah from 1994-1997 before establishing an independent laboratory dedicated to the study of gastrointestinal malignancies. I have published 35 peer-reviewed articles on my studies. Thus I have over 15 years of experience in the field of gastrointestinal malignancies. My curriculum vitae is attached to this declaration as **Exhibit A**.
3. I have reviewed the specification and current claims of the above-identified application, and the specification of U.S. Application No. 10/505,244, filed January 18, 2005.
4. I have reviewed the Office Action dated February 3, 2009, in connection with the above-identified application and the following references cited in that Office Action: Izban *et al.* (*Human Pathology* 31(12):1482-1490, 2000) and Kahn *et al.* (U.S. Patent 7,175,679). I understand that the Office Action rejected Claims 1, 8-15, 18, 21, 26-28, 37-40, 42, 53-57, and 64-72 under 35 U.S.C. § 103(a) as allegedly being obvious over Izban *et al.* in view of Kahn *et al.* Specifically, I understand that the rejection is based, at least in part, on the contention that the ordinary skilled artisan in this field would have been motivated to use the NF- $\kappa$ B inhibitor BAY-11-7085 to treat colon cancer because colon cancers are known to overexpress COX-2, which is inhibited by NF- $\kappa$ B inhibitors.
5. I have reviewed the Response and Amendment to the Office Action, which is being filed concurrently with this Declaration. I present in this Declaration evidence to support the arguments made in the accompanying Response and Amendment, which contend that the conclusions of the Office Action about the obviousness of the claims are not correct and the claims are not obvious in view of the combination of Izban *et al.* and Kahn *et al.*
6. I believe that those of skill in the art at the time of the invention would not have known that NF- $\kappa$ B was a highly sensitive target for inhibiting reseeding of cancer cells because my laboratory was the first to publish this observation in *Cancer Res.* 62:6870-6878, 2002 (published after the priority date of the present application). This reference is enclosed with the Supplemental Information Disclosure Statement as reference "D5," which is being filed concurrently with this Declaration.


7. Even if one of ordinary skill in the art were to speculate that NF- $\kappa$ B inhibition might be an effective target for inhibiting reseeding of cancer cells after transient suspension, it was not known or suggested which NF- $\kappa$ B inhibitor would be effective. Students and technicians in my laboratory and under my direction tested other known NF- $\kappa$ B inhibitors, namely, bortezomib, infliximab, and sulindac sulfide, which did not induce apoptosis of colon cancer cells during adhesion *in vitro* at doses that are known to inhibit colon cancer cell survival or proliferation. The data for bortezomib is shown in **Exhibit B**. The data for infliximab and sulindac sulfide are similar.

8. Also, the correlation asserted by the Office Action between NF- $\kappa$ B and COX-2 is not correct as the compounds recited in the current claims are not active against COX-2. A broad kinase assay of BAY 11-7082 and BAY 11-7085 was performed at Millipore at my request and the data confirmed that neither compound inhibited COX-2 at 10 $\mu$ M concentrations. Based on these studies, there is no evidence that BAY 11-7082 or BAY 11-7085 acts through inhibition of COX-2.

9. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: \_\_\_\_\_

12/23/09

  
\_\_\_\_\_  
Scott Kuwada, MD, AGAF, FACP

# **EXHIBIT A**

## CURRICULUM VITAE

### PERSONAL DATA:

- NAME: Scott K. Kuwada, MD, AGAF, FACP
- TITLE: Professor of Medicine, Chief, Division of Gastroenterology, U of Hawaii  
Adjunct Professor of Medicine & Oncological Sciences, U of Utah
- ADDRESS:  
1356 Lusitana Street  
7<sup>th</sup> Floor  
Honolulu, HI 96813
- PHONE: 808-586-2910
- FAX: 808-586-7486
- E-MAIL ADDRESS: skkuwada@hawaii.edu
- BIRTHPLACE: Wailuku, Hawaii
- CITIZENSHIP: USA
- MARITAL STATUS: Married

### EDUCATION:

- UNDERGRADUATE EDUCATION: Whitman College, B.A., 1980
- MEDICAL SCHOOL: University of Hawaii, M.S., 1985/M.D., 1988
- RESIDENCY: Internal Medicine (Categorical), Mayo Clinic, 1988-1991
- FELLOWSHIP: Gastroenterology, Mayo Clinic, 1991-1994
- BOARD CERTIFICATION: Internal Medicine, 1991; Gastroenterology, 1993, 2003

### PROFESSIONAL EXPERIENCE:

- POSITIONS:  
Research Assistant Professor of Medicine-7/1/94-2001, Dept. of Medicine,  
University of Utah  
Assistant Professor of Medicine-2001-2003, Dept. of Medicine, University of  
Utah  
Acting Chief, Division of Gastroenterology – 2001-2003, Dept. of Medicine,  
University of Utah  
Associate Professor of Medicine-2004-2008, Dept. of Medicine, University of  
Utah  
Adjunct Associate Professor of Oncological Sciences-2005-2009, University of  
Utah  
Adjunct Professor of Medicine-2008-present, University of Utah  
Professor of Medicine-Oct, 2008-present, University of Hawaii  
Chief, Division of Gastroenterology, Oct, 2008-present, University of Hawaii  
Adjunct Professor of Bioengineering, Oct, 2009-present, University of Utah
- STUDY SECTION:  
American Digestive Health Foundation – 2001-2004  
Association of International Cancer Research - 2007

National Cancer Institute Special Emphasis Panel – 2008

- EDITORIAL EXPERIENCE:

National Cancer Institute - Physician's Data Query - Cancer Genetics Editorial Board

Invited Reviewer – Gastroenterology, American Journal of Gastroenterology, Gastrointestinal Endoscopy, Journal of Clinical Gastroenterology, Mayo Clinic Proceedings, American Journal of Physiology, Cancer Research, International Journal of Cancer, Molecular Cancer Therapeutics, Clinical Cancer Research, Gut, Cancer Letters, BMC Medicine, BMC Cancer

- RESEARCH AWARDS:

CURRENT/PENDING:

NCI R01

Title: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.

Effort: PI

Award Period: resubmitted 3/5/09 (score = 181)

Cephalon

Title: Novel inhibitors of metastasis.

Role: PI

Total Direct Costs: \$2,000,000 (including indirect costs)

Award Period: 7/1/08-6/30/10

Novartis

Title: mTOR inhibitor (RAD001) therapy for treatment of intestinal polyps in Peutz-Jeghers Syndrome.

Role: PI

Total Direct Costs: \$84,000

Award Period: 5/1/08-4/30/09

NCI R01 CA40641-17A1

Title: High Risk Familial Colon Cancer: Genetics and Phenotype

Effort: gastroenterologist, 6%

Award Period: 3/1/04 –2/28/09

University of Utah Virtual Incubator Project Grant

Title: Novel inhibitors of metastasis.

Effort: PI

Total Direct Costs: \$50,000

Award Period: 2/1/08-1/31/09

Huntsman Cancer Institute Pancreas Cancer Research Group Grant

Title: Chemoprevention for pancreatic neoplasia.

Effort: PI  
Total Direct Costs: \$8,000  
Award Period: 3/1/08-2/29/09

NCI P01 CA73992-06A1  
Colorectal Cancer NCI Program Project Grant  
Molecular, Clinical Approaches to Colon Cancer Precursors  
Role: Project Co-Director  
Total Direct Costs:  
Award Period: submitted, pending review (anticipated dates: 9/12/08-8/31/13)

NCI RO1  
Title: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families  
Role: PI  
Total Direct Costs: \$2,491,434  
Award Period: submitted, pending review (anticipated dates: 9/12/08-8/31/13)

- PAST:  
Huntsman Cancer Institute Award  
Title: Integrin-modulated proliferation of colon cancer cells.  
Effort: P.I.  
Award Period: 7/1/97-6/30/99

National Institutes of Health- KO8 DK02531  
Title: Integrin modulation of proliferation in colon cancer.  
Effort: P.I.  
Award Period: 7/1/97-6/30/02

RO3 DK58094  
Title: Integrin modulation of proliferation in colon cancer.  
Effort: P.I.  
Award Period: 7/1/00-6/30/02

Cell Pathways, Grant:  
Title: Prevention of rectal polyps in adenomatous polyposis coli.  
Effort: P.I.  
Award Period: 7/1/97-02/02

Cell Pathways, Grant:  
Title: A randomized, multicenter, dose response, double blind, placebo-controlled study to determine the efficacy in causing

polyp regression and the safety of FGN-1 in patients with sporadic adenomatous polyps of the colon.

Effort: P.I.

Award Period: 2/10/98-02/02

American Digestive Health Foundation Astra-Zeneca Fellow-to-Faculty Transition Award

Effort: P.I. & Mentor

Award Period: 7/1/2001-6/30/2002

CA80852-03

Effort: DiSario (PI); Coinvestigator, 10%

Title: Chemoprevention of duodenal polyps in familial adenomatous polyposis.

Award Period: 06/01/1999-03/31/2004

Astra-Zeneca

Title: Non-clinical investigations of ZD1839 in colorectal cell lines and early disease models of colorectal cancer.

Effort: P.I., 0%

Award Period: 3/1/04-2/28/05

Dept. of Veterans Affairs Merit Review Grant

Title: Anti-epidermal growth factor receptor therapy in colon cancer.

Effort: P.I., 63%

Award Period: 10/04-09/07.

University of Utah Technology Commercialization Grant

Title: The inhibition and prevention of intraabdominal metastasis.

Effort: P.I., 0%

Award Period: 7/1/05-6/30/07

Huntsman Cancer Institute Director's Translational Research Initiative

Title: NF-kB inhibitors are a novel class of drugs that may prevent cancer seeding and metastasis

Effort: P.I., 0%

Award Period: 1/1/06-12/31/06

NCI P01 CA73992-06A1

Colorectal Cancer NCI Program Project Grant

Molecular, Clinical Approaches to Colon Cancer Precursors

Effort: gastroenterologist, 11%

Award Period: 9/12/03-8/31/08

#### HONORS:

- Academic Distinction



- Undergraduate Honors
- Grimshaw Scholar
- Signet Table
- American Gastroenterological Association & Gastroenterology Research Group Travel Award-1992
- Glaxo Institute of Digestive Health Award -1995
- American Cancer Society Institutional Award – 1995
- Fellow of the American College of Physicians – 2007
- Fellow of the American Gastroenterological Association - 2008

#### ADMINISTRATIVE EXPERIENCE:

- Retention, Promotion, and Retention Committee member, Dept. of Medicine- 7/96-6/1999, U of Utah
- Huntsman Cancer Institute, Familial Colon Cancer Clinic, Member - 7/95 – present, , U of Utah
- Division of Gastroenterology, Associate Program Director, 7/96-11-98, , U of Utah
- Division of Gastroenterology, Program Director, 11/98- 5/08, , U of Utah
- Division of Gastroenterology, Acting Division Chief, February 1, 2001-April 30, 2003, U of Utah
- Chief, Division of Gastroenterology, U of Hawaii, 10/1/08-present

#### PROFESSIONAL COMMUNITY ACTIVITIES:

- Junior League Care Fair - Volunteer Physician - 8/94 – present
- UCAN (Utah Cancer Network) –Television interviews to promote colorectal cancer screening and awareness, 2001-2002

#### MEMBERSHIPS IN PROFESSIONAL SOCIETIES:

- American College of Physicians, Fellow
- American Gastroenterological Association, Fellow
- American College of Gastroenterology, Member
- American Association for the Advancement of Science, Member
- American Society of Cell Biology, Member
- American Association of Cancer Research, Member

#### TEACHING EXPERIENCE:

- U of Utah Internal Medicine Noon residents' conference, Inflammatory Bowel Disease, 1994-2004
- U of Utah School of Medicine Gastroenterology Organ Systems Course, Inflammatory Bowel Disease, 1995-present
- U of Utah School of Medicine Gastroenterology Organ Systems Course, Malabsorption, 1995-present
- Program Director/Organizer, U of Utah Gastroenterology Multidisciplinary Conference, 1997-present
- U of Utah Physicians Assistant GI Course Faculty, 1994-present
- Undergraduate Students (Research):

- James Le – 7/2000-6/2001
  - Miryoung Kim – 9/2001-6/2002
  - Ryan Herde – 7/1/07-present
- Postgraduate Residents/Fellows (Research):
  - Rajan Khosla – 7/1998-6/2000; Current Position: Private Practice
  - Courtney Scaife, MD – 7/1999-6/2000; Current Position: Asst. Prof. of Surgery, University of Utah
  - Bradley Trowbridge, MD – 7/2000-6/2001; Current Position: Private Practice
  - Jason Wills, MD – 7/2000-6/2001; Current Position: Asst. Prof. of Medicine, University of Utah
  - Kathryn Peterson, MD – 7/2001-2002; Current Position: Asst. Prof. of Medicine, University of Utah
  - Robert Wong, MD – 7/2001-6/2002; Current Position: Asst. Prof. of Medicine, University of Utah
  - Brett Thorpe, MD – 7/2002-6/2003; Current Position: GI Fellow, University of Arizona
  - Robert Jones, MD – 7/2004-6/2005; Current Position: Private Practice
  - Brett Doxey, MD – 7/2005-6/2006; Current Position: GI Fellow, University of Utah
  - Martin Majer, MD – 7/2005-6/2007; Current Position: Hem-Onc Fellow, University of Utah
  - Changxin Xu, PhD – 11/2007-present; Current Position: Post-Doctoral Fellow, University of Utah
  - Daniel LaBarbera, PhD – 11/2007-6/2008; Current Position: Asst Prof, University of Arizona
  - Yi Shen, PhD – 8/2008-present; Current Position: Post-Doctoral Fellow, University of Utah
- Graduate Student Thesis Committee Member:
  - Graduate Student Thesis Committee Member, Monica Serban, Dept. of Pharmacology, 2005-2008
  - Graduate Student Thesis Committee Member, Mazin Al-Salihi, Dept. of Oncological Sciences, 2005-present
  - Graduate Student Thesis Committee Member, JinJin Cai, Dept. of Oncological Sciences, 2006-present
  - Graduate Student Thesis Committee Member, Matthew Powers, Dept. of Oncological Sciences, 2006-present
- Oncological Sciences Preliminary Exam –
  - Jennifer Kinsey, Stephen Lessnick Lab
  - Christopher Jones, Dean Li Lab
  - Member, Elizabeth Toomey (Molecular Biology)
  - Member, Michelle Kinsey (Molecular Biology)
  - Member, Hui Ting (Molecular Biology)

### Publications

1. Kuwada, S.K., Patel, V., Hollinger, S.B., Lin, H.J., Yarbough, P., Wiesner, R., Kaese, D., and Rakela, J. Non-A, non-B fulminant hepatitis is also non-E and non-C. *American Journal of Gastroenterology*, 1994; 89(1): 57-61.
2. Kuwada, S.K. and Alexander, G.L. The long-term outcome of endoscopic dilation of nonmalignant pyloric stenosis. *Gastrointestinal Endoscopy*, 1995; 41: 15-17.
3. Kuwada, S.K. and Burt, R.W. The genetics of colon cancer. *Current Opinion in Gastroenterology*, 1996; 12(1): 8-11.
4. Kuwada, S.K. and Burt, R.W. The clinical features of the hereditary and nonhereditary polyposis syndromes. *Surgical Oncology Clinics of North America*, 1996; 5(3): 553-567.
5. Kuwada, S.K., Balm, R.A., and Gostout, C.J. The risk of withholding chronic anticoagulation due to acute gastrointestinal bleeding. *American Journal of Gastroenterology*, 1996; 91: 1116-1119.
6. Rodriguez-Larrain, J.M., Ziebert, J.J., Kfoury, A.G., Kuwada, S., Taylor, D.O., and Renlund, D.G. Incidence of adenomatous colorectal polyps in cardiac transplant recipients. *Transplantation*, 1997; 64(3): 528-530.
7. Kuwada, S.K., Lund, K.A., Cliften, P., Amsler, K., Opresko, L.K., and Wiley, H.S. Differential regulation and signaling of apical versus basolateral epidermal growth factor receptors in polarized epithelial cells. *American Journal of Physiology*, 1998; 275(6, part 1): C1419-1428.
8. Amsler, K. and Kuwada, S.K. Membrane receptor location defines receptor interaction with signaling proteins in a polarized epithelium. *American Journal of Physiology*, 1999, 276(1, part 1): C91-101.
9. Damstrup, L., Kuwada, S.K., Dempsey, P.J., Brown, C.L., Hawkey, C.J., Poulsen, H.S., Wiley, H.S., and Coffey, R.J. Jr. Amphiregulin acts as an autocrine growth factor in two human polarizing colon cancer lines that exhibit domain selective EGF receptor mitogenesis. *British Journal of Cancer*, 1999, 80(7): 1012-1019.
10. Kuwada, S.K., Li, X.F., Damstrup, L., Dempsey, P.J., Coffey, R.J., and Wiley, H.S. The dynamic expression of the epidermal growth factor receptor and epidermal growth factor ligand family in a differentiating intestinal epithelial cell line. *Growth Factors*, 1999, 17(2): 139-153.

11. Kuwada SK. Colorectal cancer 2000. Education and screening are essential if outcomes are to improve. *Postgrad Med*, 2000, 107(5):96-8, 101-4, 107.
12. Fox JR, Kuwada SK. Today's approach to esophageal cancer. What is the role of the primary care physician? *Postgrad Med*, 2000, 107(5):109-114.
13. Kuwada, S.K. and Li, X.F. Integrin  $\alpha 5/\beta 1$  mediates fibronectin-dependent epithelial cell proliferation through epidermal growth factor receptor activation. *Mol. Biol. Cell*, 2000, 11: 2485-2496
14. Tumbapura, A., Kuwada, S., and DiSario, J.A. Adenocarcinoma of the Small Intestine. *Current Treatment Options in Gastroenterology*, 2000, 3 (1): 51-57.
15. Kuwada, S.K. Carcinoid tumors. *Semin Gastrointest Dis*. 2000, 11(3): 157-61.
16. Kuwada, S.K. and Burt, R.W. Prevention of colorectal cancer. *European Journal of Surgery*, 2001, 167(suppl 586): 40 – 42.
17. Clayton F, Kotler DP, Kuwada SK, Morgan T, Stepan C, Kuang J, Le J, Fantini J. Gp120-Induced Bob/GPR15 Activation : A Possible Cause of Human Immunodeficiency Virus Enteropathy. *Am J Pathol*. 2001 159(5):1933-1939.
18. Wills, J.C., Kuwada, S.K., and Burt, R.W. "Hot spots" can burn you. *Am J Gastroenterol* 2002, 97(3): 757-758.
19. Scaife CL, Kuang J, Wills JC, Trowbridge DB, Gray P, Manning BM, Eichwald EJ, Daynes RA, Kuwada SK. Nuclear Factor kappaB inhibitors induce adhesion-dependent colon cancer apoptosis: implications for metastasis. *Cancer Res*. 2002; 62(23): 6870-6878.
20. Rice, P.L., Kelloff, J., Sullivan, H., Driggers, L.J., Beard, K.S., Kuwada, S., Piazza, G., and Ahnen, D.J. Sulindac metabolites induce caspase- and proteasome-dependent degradation of beta-catenin protein in human colon cancer cells. *Mol Cancer Ther*, 2003; 2(9): p. 885.
21. Kuwada, S.K., Scaife, C.L., Kuang, J., Li, X., Wong, R.F., Florell, S.R., and Gray, P.D.. Effects of trastuzumab on EGFR-dependent and -independent human colon cancer cells. *Int. J. Cancer* 2004; 109(2): 291-301.
22. Neklason, D.W., Solomon, C.H., Dalton, A.L., Kuwada, S.K., and Burt, R.W. Intron 4 mutation in APC gene results splice defect and attenuated FAP phenotype. *Familial Cancer*, 2004; 3 (1): 35-40.
23. Burt RW, Leppert MF, Slaterry ML, Samowitz WS, Spirio LN, Kerber RA, Kuwada SK, Neklason DW, DiSario JA, Lyon E, Hughes JP, Chey WY, White

- RL. 2004. Genetic Testing and Phenotype in a Large Kindred with Attenuated Familial Adenomatous Polyposis. *Gastroenterology*, 2004; 127: 444-451.
24. Wong, R.F., Khosla, R., Moore, J.G., and Kuwada, S.K. Colonoscopy in young patients with hematochezia. *J Fam Pract*, November 1, 2004; 53(11): 879-84.
25. Kuwada, S.K., Kuang, J., and Li, X. Integrin  $\alpha 5/\beta 1$  expression mediates HER-2 downregulation in colon cancer cells. *J Biol Chem*. 2005 May 13;280(19):19027-35.
26. Doxey, B.W., Kuwada, S.K., and Burt, R.W. Inherited Polyposis Syndromes: Molecular Mechanisms, Clinicopathology, and Genetic Testing. *Clinical Gastroenterology and Hepatology*, 2005;3:633– 641
27. Arber, N., Kuwada, S., Leshno, M., Sjodahl, R., Hultcrantz, R., and Rex, D. Sporadic Adenomatous Polyp Regression with Exisulind is Effective but Toxic: A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study *Gut*. 2006 Mar;55(3):367-73.
28. Maul, J.S., Warner, N.R., Kuwada, S.K., Burt, R.W., and Cannon-Albright, L.A.. Extracolonic Cancers Associated With Hereditary Nonpolyposis Colorectal Cancer in the Utah Population Data Base. *Am J Gastroenterol*. 2006 Jul;101(7):1591-6.
29. Jones, R.G., Li, X., Gray, P.D., Kuang, J., Clayton, F., Samowitz, W.S., Madison, B.B., Gumucio, D.L., and Kuwada, S.K. Conditional deletion of  $\beta 1$  integrin in the intestinal epithelium causes a loss of Hedgehog expression, intestinal hyperplasia, and early postnatal lethality. *J Cell Biol*. 2006 Nov 6;175(3):505-514.
30. Ferrández, A., Pho, L., Solomon, C., Samowitz, W.S., Kuwada, S.K., Knecht, T.P., Gilfeather, M., and Burt, R.W. An evidence-based multidisciplinary approach to the clinical considerations, management and surveillance of adrenal lesions in familial adenomatous polyposis. *Dis Colon Rectum*. 2006 Nov; 49(11): 1781-90.
31. Kuwada, S.K. Drug evaluation: Volociximab, an angiogenesis-inhibiting chimeric monoclonal antibody. *Curr Opin Mol Ther*. 2007 Feb;9(1):92-8.
32. Mackenzie, S.H., Fang, J., and Kuwada, S.K. Severe upper gastrointestinal bleeding in a patient with percutaneous gastrostomy tube placement by the push method. *Gastrointest Endosc*. 2007 Mar 22; 65(6):935-7.
33. Mackenzie SH, Go M, Chadwick B, Thomas K, Fang J, Kuwada S, Lamphier S, Hilden K, Peterson K. Eosinophilic oesophagitis in patients presenting with dysphagia--a prospective analysis. *Aliment Pharmacol Ther*. 2008 Nov

1;28(9):1140-6.

34. Kuwada, S.K., Tumbapura, A., Thorpe, B., Kerber, R., Samowitz, W., McDonald, J. Hoyle, C., Mineau, G., Fang, J., Burt, R.W. The characteristics of non-familial polyposis, non-hereditary nonpolyposis familial colorectal cancer. *Am J Gastroenterol.* 2008 Oct;103(10):2577-84.
35. Daniel V. LaBarbera, Katarzyna Modzelewsk, Amanda I. Glazar, Phillip D. Gray, Manjinder Kaur, Tong Liu, Douglas Grossman, Mary Kay Harper, Scott K. Kuwada, Nadeem Moghal, Chris M. Ireland. The marine alkaloid naamidine A promotes caspase-dependent apoptosis in tumor cells. Accepted for publication in *Anticancer Research*.
36. Doxey, B., Gray, P.D., and Kuwada, S.K. Restoration of juxtacrine death receptor - induced apoptosis of cancer cells through BAY 11-7085-mediated inhibition of c-FLIP abrogates peritoneal carcinomatosis. Submitted
37. Majer, M., Li, X., Kuang, J., and Kuwada, S.K. The effects of conditional deletion of *erbB2* in a mouse model of pancreatic tumorigenesis. Submitted
38. Xu Changxin, Li, X., Gray, P.D., and Kuwada, S.K.  $\beta 1$  integrins regulate Hedgehog expression in an ErbB-dependent fashion. In Preparation
39. Kuang, J., Li, X., Majer, M., and Kuwada, S.K. HER-2 interacts with the atypical histone macroH2A in cancer cells. In Preparation
40. Deborah W. Neklason, Therese M. Tuohy, Jeffery Stevens, Brith Otterud, Lisa Baird, Richard A. Kerber, Wade S. Samowitz, Scott K. Kuwada, Mark F. Leppert, Randall W. Burt Colorectal adenomas and cancer link to chromosome 13q22.1-13q31.3 in a large family with excess colorectal cancer. Submitted

### Book Chapters & Invited Reviews

1. Kuwada, S.K., Neklason, D., and Burt, R.W. Biology and Molecular Genetics of Colorectal Cancer, in *Colorectal Cancer: Multimodality Management*, Ed. Leonard B. Saltz, Humana Press, Inc.
2. Wong, R.F., Kuwada, S., Burt, R.W. Hereditary colorectal cancer. *Colonoscopy Principles and Practice*, Ed. Jerome D. Waye, Douglas K. Rex, and Christopher B. Williams (2003).

3. Majer, M. and Kuwada, S.K. Targeting the epidermal growth factor receptor family in gastrointestinal malignancies. *Recent Advances in Gastrointestinal Carcinogenesis*, Ed. Hiromi Bamba and Shinichi Ota (2006), 163-180.
4. Majer, M., Kuwada, S.K., and Akerley, W. Colorectal cancer chemotherapy. *Anti-Cancer Agents in Medicinal Chemistry* (2007), in press.
5. Kuwada, S.K. Volociximab Evaluation. Thomson Scientific Limited (2007), in press.
6. Doxey, B.W. and Kuwada, S.K. Hereditary nonpolyposis colon cancer: Revised Bethesda criteria, immunohistochemistry, microsatellite instability, germline analysis, and emerging issues in genetic testing. *Current Colorectal Cancer Reports* (2007) 3(1): 10-15.

### Abstracts

1. Kuwada, SK, Ahlquist, DA, Cha, S, Wieand, HS, McGill, DR, Moertel, CG. Heritable features of common colorectal neoplasia. 1992. *Gastroenterology* 1892; 102(4, part 2): A370.
2. Kuwada, SK, Alexander, GL. The long-term outcome of endoscopic dilatation of nonmalignant pyloric stenosis. *American Journal of Gastroenterology* (1992)87: 113A.
3. Kuwada, SK, Kames, WE, Jr, Maihle, NJ. A 36-kilodalton phosphoprotein binds to the carboxy-terminus of the c-erbB1 oncogene product. (1993) *Gastroenterology*; 104: 418A.
4. Kuwada, SK, Rakela, J, Patel, V, Hollinger, SB, Lin, HJ, Yarbough, P, Wiesner, R, Kaese, D. Non-A, non-B fulminant hepatitis is also non-E and non-C. (1993) *American Journal of Gastroenterology*; 88: 285A.
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6. Kuwada, SK, Balm, RA, Gostout, CJ. Gastrointestinal bleeding in the anticoagulated patient: risk of withholding and resuming anticoagulants. (1994) *American Journal of Gastroenterology*; 89: 382A.
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20. Tumbapura, A., Thorpe, B., Kerber, R., Samowitz, W., McDonald, J. Hoyle, C., Mineau, G., Burt, R.W., Kuwada, S.K. Colonic neoplasia incidence is elevated later in life in familial colorectal cancer. DDW 2000, San Diego, CA
21. Kuwada, S.K. and Li, X.F. The epidermal growth factor receptor mediates fibronectin-induced epithelial cell proliferation and survival. DDW 2000, San Diego, CA
22. Andrew D. Coen and Scott K. Kuwada. Stroke as a consequence of solitary rectal ulcer syndrome. Am J Gastroenterol 1 Sep 2003 98(9S): p. S203.
23. DiSario, J.A., Ogara, M.M., Szabo, A., Kuwada, S., Gray, P. Exisulind for Duodenal Adenomas in Persons with Familial Adenomatous Polyposis. World Congress of Gastroenterology 2005, Toronto, Canada.
24. Doxey, B.W., Gray, P.D., Kuwada, S.K. Inhibition of nuclear factor kB inhibits cancer cell implantation *in vivo*. Digestive Diseases Week 2006, Annual Meeting of the American Gastroenterological Association, Los Angeles, CA.
25. Jones, R., Li, X., Gray, P., Clayton, F., Samowitz, W., Kuwada, S.K. Conditional deletion of beta 1 integrins in the intestinal epithelium reveals their novel role in the regulation of the epithelial stem cell compartment through Hedgehog signaling. Stem Cells in Gastrointestinal Development, Regeneration and Neoplasia, September 8-9, 2006, Tyson's Corner, Virginia.

### Oral Presentations

1. Heritable features of common colorectal neoplasia. Oral presentation at Digestive Disease Week and the 93rd Annual Meeting of the American Gastroenterological Association, San Francisco, California, May 9-15. 1994
2. Kuwada, SK, Rakela, J, Patel, V, Hollinger, SB, Lin, HJ, Yarbough, P, Wiesner, R, Kaese, D. Non-A, non-B fulminant hepatitis is also non-E and non-C. Oral presentation at the 1993 American College of Gastroenterology meeting, New York, New York
3. Kuwada, SK, Burt, R, Mayle, M, Slattery, M, Kerber, R, DiSario, J, Biorkman, D, Khullar, S, Samowitz, W, White, R, Leppert, M. The proximal predominance of colonic adenomas in attenuated adenomatous polyposis coli. Oral presentation at the 1995 Annual Meeting of the American Gastroenterological Association, San Diego, CA

4. Kuwada, S.K., Wiley, H.S., and Lund, K. Compartmentalization of growth factor-mediated signal transduction in polarized epithelial cells. 1997 Annual Meeting of the American Gastroenterological Association, Washington, D.C.
5. Burke, C., Arber, N., Phillips, R., Hultcrantz, R., Bjork, J., Syngal, S., Rodriguez, M., Luchtefeld, M., Alin Botomon, V., Wruble, L., Kuwada, S. Exisulind continues to prevent colonic adenoma formation in familial adenomatous polyposis patients treated for 18 months. 2000 Annual Meeting of the American Gastroenterological Association, San Diego, CA
6. Burke, C., van Stolk, R., Arber, N., Hultcrantz, R., Bjork, J., Syngal, S., Rodriguez, M., Luchtefeld, M., Alin Botomon, V., Wruble, L., Kuwada, S., and S. Phillips, R. Exisulind prevents adenoma formation in familial adenomatous polyposis. Digestive Disease Week, Annual Meeting of the American Gastroenterological Association 2000, San Diego, CA
7. Kuwada, S.K., Tumbapura, A., Thorpe, B., Kerber, R., Mineau, G., Samowitz, W., Fang, J., Hoyle, C., McDonald, J., Burt, R.W. The colonic phenotype of non-FAP, non-HNPCC familial colorectal cancer. 3<sup>rd</sup> Joint Meeting – Leeds Castle Polyposis Group and International Collaborative Group Hereditary Non-Polyposis Colorectal Cancer, April, 2001, Venice, Italy
8. Kuwada, S.K., Trowbridge, D.B., Eichwald, E.J., Kuang, J., Gray, P., Daynes, R. Colon cancer cell adhesion stimulates NF-kB mediated survival. Digestive Diseases Week 2002, Annual Meeting of the American Gastroenterological Association, San Francisco, CA
9. Arber, N., Rex, D., Sjodahl, R., Hultcrantz, R., Kuwada, S. Exisulind induced regression of sporadic adenomatous polyps in a randomized double-blind, placebo controlled trial. Digestive Diseases Week 2002, Annual Meeting of the American Gastroenterological Association, San Francisco, CA
10. Kuwada, S.K., Wong, R.F., Kuang, J., Li, X., and Gray, P. Integrin-mediated downregulation of HER-2 in colon cancer cells. Digestive Diseases Week 2003, Annual Meeting of the American Gastroenterological Association, Orlando, FL
11. Kuwada, S.K., Thorpe, B., Ferrandez, A., Tumbapura, A., Samowitz, Hoyle, C., Neumeister, B., Venne, V., W., Fang, J., Kerber, R., Mineau, G., and Burt, R.W. Common Familial Colon Cancer (CFCRC). 4<sup>th</sup> Joint Meeting of the Leeds Castle Polyposis Group and International Collaborative Group for Hereditary Non-Polyposis Colorectal Cancer. September, 2003, Cleveland, OH.
12. Kuwada, S.K., Kuang, J., Li, Xiufen. Integrin alpha 5/beta 1 regulates HER-2 expression in colon cancer cells. Digestive Diseases Week 2005, Annual Meeting of the American Gastroenterological Association, Chicago, IL

13. Jones, R., Li, X., Gray, P., Clayton, F., Samowitz, W., Kuwada, S.K. Conditional deletion of beta 1 integrin in intestinal epithelium. Digestive Diseases Week 2005, Annual Meeting of the American Gastroenterological Association, Chicago, IL
14. Jones, R., Li, X., Gray, P., Clayton, F., Samowitz, W., Kuwada, S.K. Beta 1 integrins regulate proliferation and Wnt signaling in the intestinal epithelium. Digestive Diseases Week 2006, Annual Meeting of the American Gastroenterological Association, Los Angeles, CA
15. Li, X, Gray, P, Clayton, F, Samowitz, W, Kuwada, SK. Regulation of intestinal epithelial proliferation through integrin beta 1-dependent paracrine signaling in intestinal stromal cells. Digestive Diseases Week 2008, Annual Meeting of the American Gastroenterological Association, Chicago, IL
16. Majer, MM, Gray, P, Li, X, Emerson, L, Kuwada, SK. Conditional deletion of Erbb2/Neu inhibits pancreatic tumorigenesis. Digestive Diseases Week 2008, Annual Meeting of the American Gastroenterological Association, San Diego, CA
17. Kuwada, SK. Genetics of colorectal cancer syndromes. Digestive Diseases Week 2008, Annual Meeting of the American Gastroenterological Association, San Diego, CA

### **Visiting Professor/Invited Speaker**

1. Society of Gastroenterological Nurses and Associates, Regional Meeting: "Screening for colorectal cancer," 1998, Snowbird, UT
2. Annual Meeting of the American College of Physicians, Distinguished Lecturer,: "Gastrointestinal Cancer 1999," New Orleans, LA
3. Annual Meeting of the American Gastroenterological Association, Digestive Diseases Week, Meet the Investigator: "The Genetics of Colon Cancer." 1999, Orlando, FL
4. Current Topics in Gastroenterology: "Colon Cancer Prevention," 1999, Paradise Island, Bahamas
5. University of Utah Advances in Internal Medicine 2000: "New Agents for Inflammatory Bowel Disease" and "Pathogenesis of Colon Cancer," Park City, Utah

6. Gastrointestinal Cancer: A Multidisciplinary Approach for the Clinician, University of Utah & University of California San Francisco: "Carcinoid Tumors of the GI Tract," 2000, Park City, Utah
7. Visiting Professor, Vanderbilt University, Dept. of Medicine, Div. of Gastroenterology: "Fibronectin-induced epithelial cell proliferation is mediated by the epidermal growth factor receptor," Sept. 26, 2000
8. Visiting Professor, Mayo Clinic, Dept. of Medicine, Div. of Gastroenterology: "Research Funding for Young Investigators," October 7, 2000
9. 2000 Triad Meeting (American Cancer Society, American College of Surgeons, & Utah Cancer Registrars' Association), "Current Guidelines for Early Detection & Prevention of Colorectal Cancer," Saturday, Salt Lake City, Utah, October 14, 2000
10. Tooele Valley Medical Center, Medical Grand Rounds: "Colon Cancer Screening," Tooele, Utah, October 19, 2000
11. Visiting Professor, University of Chicago, Dept. of Medicine, Div. of Gastroenterology: "Crosstalk between integrins and growth factor receptors involved in fibronectin-dependent proliferation in intestinal epithelial cells," March 8, 2001
12. Gastrointestinal Cancer: A Multidisciplinary Approach for the Clinician, University of Utah & University of California San Francisco: "Colon cancer genetics," 2001, Park City, Utah
13. Colon cancer: genetic testing. Annual Meeting of the American College of Gastroenterology, Sept. 2001, Las Vegas, NV
14. Signal Transduction. Annual Scientific Meeting of the American College of Veterinary Pathologists. December, 2001, Salt Lake City, Utah
15. Gastrointestinal Cancer: A Multidisciplinary Approach for the Clinician, University of Utah & University of California San Francisco: "Colon cancer genetics," 2002, Park City, Utah
16. Sunrise Medical Center Medical Grand Rounds: Colon Cancer Screening and Genetic Testing. June, 2002, Las Vegas, NV
17. Current colorectal cancer screening guidelines and the hereditary colon cancer syndromes. State of the Art Colorectal Cancer Care. April, 2003, Salishan Resort, Gleneden Beach, Oregon

18. Gastrointestinal Cancer: A Multidisciplinary Approach for the Clinician, University of Utah & University of California San Francisco: "Colon cancer genetics for the clinician," 2003, Park City, Utah
19. Basic Research Advances in Colon Cancer. Digestive Diseases Week 2003, Annual Meeting of the American Gastroenterological Association, Orlando, FL
20. Visiting Professor, Vanderbilt University, Dept. of Medicine, Div. of Gastroenterology, Nashville, TN: "The role of HER-2 in colorectal cancer," June 24, 2003
21. Visiting Professor, Mayo Clinic, Dept. of Medicine, Div. of Gastroenterology, Rochester, MN: "Aberrant signaling pathways present rational therapeutic targets in colorectal cancers." Nov. 17, 2003.
22. Visiting Professor, Vanderbilt University, Cell Biology and GI Cancer Program, Nashville, TN: "Insights into epithelial-mesenchymal interactions through conditional gene deletion in the intestinal epithelium." 4/19/2005
23. 9<sup>th</sup> Annual Meeting of the Collaborative Group of the Americas on Inherited Colorectal Cancer, November, 2005, Salt Lake City, Utah, "Chemoprevention of Hamartomatous Polyposis Syndromes"
24. 9<sup>th</sup> Annual Meeting of the Collaborative Group of the Americas on Inherited Colorectal Cancer, November, 2005, Salt Lake City, Utah, "Rare tumors of the hereditary nonpolyposis colorectal cancer syndrome"
25. Visiting Professor, University of Kansas School of Medicine, Division of Gastroenterology, Kansas City, Kansas, October 17, 2006: "State of the Art in Colorectal Cancer Chemoprevention."
26. Visiting Professor, University of Kansas School of Medicine, Medicine Grand Rounds, Kansas City, Kansas, October 18, 2006: "Familial Colorectal Cancer & the Advent of Molecular Medicine."
27. Visiting Professor, University of Kansas School of Pharmacy, Kansas City, Kansas, October 18, 2006: "Conditional deletion of beta 1 integrin reveals its role in the regulation of intestinal proliferation and homeostasis."
28. Visiting Professor, The Queen's Medical Center, Honolulu, Hawaii, Jan. 9, 2007, Medical Grand Rounds: "Colorectal Cancer Genetics."
29. Visiting Professor, University of Hawaii School of Medicine, Jan. 10, 2007, Cell & Molecular Biology Seminar Series: "Beta 1 integrins mediate intestinal epithelial proliferation and homeostasis through Hedgehog expression and signaling."

30. Visiting Professor, Fred Hutchinson Cancer Center, June, 2007, Conditional deletion of beta 1 integrin in the intestinal epithelium disrupts intestinal homeostasis.
31. Invited Speaker, 13<sup>th</sup> Annual Collaborative Group of the Americas on Inherited Colorectal Cancer Meeting, Honolulu, Hawaii, Oct. 17-18, 2009, Hyperplastic Polyposis: operative –vs- non-operative therapy.
32. Invited Speaker, 13<sup>th</sup> Annual Collaborative Group of the Americas on Inherited Colorectal Cancer Meeting, Honolulu, Hawaii, Oct. 17-18, 2009, A rational chemoprevention strategy for Peutz-Jeghers Syndrome.

# **EXHIBIT B**

**Su.86.86 CD133+ Cells Treated with BAY 11-7085  
and Bortezomib for 5 Hrs. in Co-culture**

